Occurrence of Neural Tube Defects and Down Syndrome Among Siblings

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Abstract

A recent study had reported increased risk of Down syndrome among siblings of infants with neural tube defects (NTDs) and vice versa. However, Hawaii Birth Defects Registry data indicate no elevated risk of Down syndrome among older siblings of infants with NTDs and vice versa, contradicting the findings of the previous study. Further investigation of the potential relationship is warranted.

Introduction

A number of studies have found reduced risk of neural tube defects (NTDs) with maternal periconceptional use of folic acid.[1] This association has been linked to polymorphisms in genes for folate metabolism such as 5,10-methylenetetrahydrofolate reductase (MTHFR) and methionine synthase reductase (MTRR).[2-5] Several investigations have likewise noted a relationship between mutations in MTHFR and MTRR genes and Down syndrome,[6-9] although other investigations reported no such association.[10,11] Folic acid is a component of DNA synthesis. If DNA synthesis is impaired, then there may be problems in the segregation of chromosomes during cell division, leading to aneuploidies such as Down syndrome. Impairment of DNA synthesis also could interfere with rapid cell division during the early development of the fetus, resulting in structural defects such as NTDs.

The observation that both NTDs and Down syndrome may be influenced by polymorphisms in the same folate metabolism genes suggests a similar etiology for at least a portion of these two birth defects. One recent study demonstrated an elevated risk of Down syndrome among siblings of infants with NTDs and vice versa.[12] However, an accompanying editorial mentioned several limitations to this study.[13] The study was hospital-based, and risk for conditions in hospital-based studies may be exaggerated when compared to population-based studies. Moreover, the reference rates for NTDs and Down syndrome that were used were from other populations. The results of a subsequent hospital-based investigation did not support the findings of the original study.[14] The intent of the present investigation was to determine the risk of Down syndrome among older siblings of infants and fetuses with NTDs and vice versa using data from a population-based birth defect registry and reference rates from the population being studied.

Methods

Data for this analysis was obtained from the Hawaii Birth Defect Program (HBDP), a population-based birth defects registry for the state of Hawaii. HBDP staff identify eligible infants and fetuses (any pregnancy outcome with one or more reportable birth defect identified between conception and one year after delivery where the pregnancy ended in Hawaii) and collect information through review of logs and medical records at all delivery and tertiary care pediatric hospitals, facilities that perform elective terminations secondary to fetal anomalies, genetic counseling centers, cytogenetic laboratories, and all but one major prenatal ultrasound facility in the state. Through its multiple source ascertainment system, the ascertainment of eligible infants and fetuses by the HBDP is believed to be as complete as possible.

Among the information the HBDP collects is the total number of older siblings. This information generally is available in the medical records the HBDP staff review as a mention of the total parity or gravidity or a list of all previous pregnancies. The HBDP also collects the history of birth defects among older siblings. The manner in which this is done is described elsewhere.[15] Briefly, birth defects among older siblings are identified through review of the medical records of the probands as well as review of the medical records of any older siblings mentioned to have birth defects where possible. The HBDP database is also examined to identify multiple infants or fetuses with the same mother and/or father.

Cases were all infants and fetuses with Down syndrome confirmed by cytogenetic analysis or NTDs delivered during 1986-2000. Reference rates for the two birth defects were calculated based on the 281,866 live births delivered in Hawaii during 1986-2000. The total number of older siblings of any pregnancy outcome were determined for each birth defect. The number of older siblings with an NTD was determined for Down syndrome cases and the number of older siblings with Down syndrome was determined for NTD cases. The observed number of older siblings with the birth de-

fect in question was then compared with the expected number based on the reference rate. P-values and 95% confidence intervals (CIs) were calculated using Poisson probability. P-values less than or equal to 0.05 or 95% CIs that did not include 1.0 were considered to indicate that the observed number of older siblings with a particular birth defect was significantly different than expected.

Results

During 1986-2000, there were 286 infants and fetuses with NTDs and 441 with Down syndrome, resulting in reference rates of 10.1 per 10,000 live births for NTDs and 15.6 per 10,000 live births for Down syndrome.

The number of older siblings was known for 284 NTD cases, of which 205 had one or more older siblings. A total of 496 older siblings was identified. None of the older siblings were reported to have Down syndrome, which is not significantly different from the 0.77603 siblings that were expected based on the reference rate (P=0.460; 95% CI 0.00-4.75).

The number of older siblings was identified for 432 cases of Down syndrome, and 362 of these cases had one or more older siblings. There was a total of 981 older siblings. One older sibling had an NTD (encephalocele). This is not significantly different from the 0.99539 older siblings with NTDs that were expected based on the reference rate (P=0.630, 95% CI 0.03-5.60).

Discussion

Using population-based data and reference rates from the study population, we failed to find increased risk of Down syndrome among older siblings of infants and fetuses with NTDs and vice versa. This is contrary to the findings of a previous study,[12] although consistent with a subsequent investigation.[14]

Our investigation also has limitations. Since the maternal age at the previous pregnancies was not known, a maternal age-adjusted expected number of Down syndrome births could not be calculated. In addition, the medical records of all older siblings were not reviewed, only those where there had been report of a birth defect in the records of the proband and the siblings' medical records could be found, and those that were in the HBDP database. Thus some birth defects among siblings might be missed. It is unknown to what degree this will impact the investigation. However, the data in other population-based birth defects registries will likely suffer from the same limitation. Finally, the relatively small number of cases and older siblings limits the statistical significance of the analysis; thus, this investigation has limited power. This study may be considered a pilot. Since some birth defects registries in other states also may collect information on birth defects among family members,[16] other birth defects registries with larger populations may repeat this analysis. Furthermore, the data presented here may be combined with data from other population-based birth defects registries in meta-analyses that allow for greater statistical significance.

Considering that the results of our investigation differ from that of the original study,[12] further investigation into the potential link between NTDs and Down syndrome is warranted.

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